

1. (Currently amended) A [[L]] liquid pharmaceutical formulation for the prolonged release of active principle(s) (AP), ~~this said~~ formulation comprising an aqueous colloidal suspension of low viscosity based on submicronic particles of water-soluble biodegradable polymer [PO] [[(PO)]] carrying hydrophobic groups [HG] [[(HG)]], said submicronic particles being non-covalently associated with at least one active principle (AP), wherein characterized in that:

[[the]] a dispersion medium of the suspension comprises ~~consists essentially of~~ water~~[[.]]~~;

~~said formulation is capable of being injected parenterally and~~

said formulation forms then forming a gelled deposit *in vivo* when injected parenterally and this formation of a gelled deposit~~[[.]]~~ ;

~~on the one hand being~~ wherein said formulation is at least partly caused by at least one physiological protein present *in vivo*~~[[.]]~~ ;

~~and on the other hand making it possible to~~ prolongs and controls the *in vivo* release time of the AP beyond 24 h after administration~~[[.]]~~ ;

[[it]] is liquid under the injection conditions~~[[.]]~~ ;

and [[it]] is [[also]] liquid at the physiological temperature and/or at the physiological pH and/or in the presence of:

a physiological electrolyte in a physiological concentration,

and/or at least one surfactant.

2. (Currently amended) [[F]] The formulation according to claim 1, characterized in that its concentration of [PO] is set at a ~~sufficiently high to~~ value that allows the formation of a gelled deposit *in vivo* after parenteral injection, in the presence of at least one physiological protein.

3. (Currently amended) A [[L]] liquid pharmaceutical formulation for the prolonged release of active principle(s) (AP), this formulation:

a) being liquid in the ambient atmosphere~~[[.]]~~ ;

b)[[also]] being liquid at the physiological temperature and/or at the physiological pH and/or in the presence of:

a physiological electrolyte in a physiological concentration,

and/or at least one surfactant~~[[,]]~~ ;

~~c)~~ and comprising an aqueous colloidal suspension of low viscosity based on submicronic particles of water-soluble biodegradable polymer [PO] carrying hydrophobic groups [HG], said particles being non-covalently associated with at least one active principle AP, and the dispersion medium of the suspension ~~comprises consisting essentially of water,~~ characterized in that its concentration of [PO] is set at a ~~sufficiently high to value~~ that allows the formation of a gelled deposit *in vitro*, in the presence of at least one protein.

4. (Currently amended) ~~[[F]] The formulation according to claim 1, any one of the preceding claims, characterized in that its~~ wherein the concentration of [PO] is such that:

$[PO] \geq 0.9.C1,$

~~preferably $20.C1 \geq [PO] \geq C1,$~~

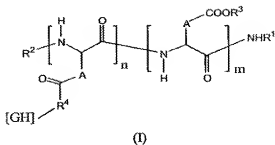
~~and particularly preferably $10.C1 \geq [PO] \geq C1,$~~

where C1 is the “induced gelling” concentration of the particles of PO, as measured in an IG test.

5. (Currently amended) ~~[[F]] The formulation according to claim 1 any one of the preceding claims, characterized in that its~~ wherein said formulation has a viscosity ~~[[is]]~~ less than or equal to 5 Pa.s.

6. (Currently amended) ~~[[F]] The formulation according to claim 1 any one of the preceding claims, characterized in that~~ wherein the polymer [PO] is a polyamino acid formed of aspartic units and/or glutamic units, at least ~~one of said some of these~~ units carrying grafts containing at least one hydrophobic group [HG] ~~[[HG]]~~.

7. (Currently amended) ~~[[F]] The formulation according to claim 6, characterized in that the~~ [PO] is ~~[[are]]~~ defined by general formula (I) below:



in which:

R^1 is selected from the group consisting of: H, a linear C2 to C10 alkyl or branched C3 to C10 alkyl, benzyl, a terminal amino acid unit and $[[\text{or}]] -R^4\text{-[HG]}$;

R^2 is selected from the group consisting of: H, a linear C2 to C10 acyl or branched C3 to C10 acyl group, a pyroglutamate and $[[\text{or}]] -R^4\text{-[HG]}$;

R^3 is selected from the group consisting of: H and $[[\text{or}]]$ a cationic entity preferably selected from the group consisting of comprising:

metal cations advantageously selected from the subgroup consisting of comprising sodium, potassium, calcium and magnesium,
organic cations advantageously selected from the subgroup consisting of comprising:
cations based on amine,
cations based on oligoamine,
cations based on polyamine (polyethylenimine being particularly preferred), and
cations based on amino acid(s) advantageously selected from the class consisting of comprising: cations based on lysine or arginine,
and cationic polyamino acids advantageously selected from the subgroup comprising polylysine and oligolysine;

R^4 is a direct bond or a spacer based on 1 to 4 amino acid units;

A independently is a radical $-\text{CH}_2\text{--}$ (aspartic unit) or $-\text{CH}_2\text{--CH}_2\text{--}$ (glutamic unit);

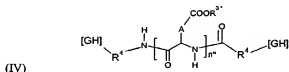
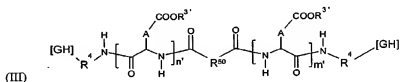
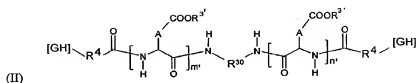
$n/(n+m)$ is defined as the molar grafting rate and its value is sufficiently low for $[\text{PO}]$, dissolved in water at pH 7 and at 25°C, to form a colloidal suspension of submicronic particles of $[\text{PO}]$, $n/(n+m)$ preferably being between 1 and 25 mol % and particularly preferably between 1 and 15 mol %;

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$n + m$ varies from 10 to 1000 and ~~preferably between 50 and 300~~;

[HG] is a hydrophobic group.

8. (Currently amended) [[F]] The formulation according to claim 6, characterized in that the [PO] has ~~(have)~~ one of general formulae (II), (III) and (IV) below:



in which:

[HG] is a hydrophobic group;

R^{30} is a linear C2 to C6 alkyl group;

R^7 is H or a cationic entity ~~preferably~~ selected from the group comprising:

metal cations ~~advantageously~~ selected from the subgroup

comprising consisting of sodium, potassium, calcium and magnesium,

organic cations ~~advantageously~~ selected from the subgroup

comprising consisting of: cations based on amine, cations based on oligoamine, cations based on polyamine (polyethylenimine being particularly preferred), and cations based on amino acid(s)

~~advantageously~~ selected from the class comprising cations based on lysine or arginine, and cationic polyamino acids ~~advantageously~~ selected from the subgroup comprising polylysine and oligolylysine;

R^{30} is a C2 to C6 alkyl, dialkoxy or diamine group;

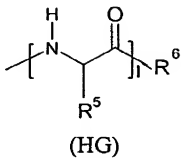
R^4 is a direct bond or a "spacer" based on 1 to 4 amino acid units;

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A independently is a radical -CH₂- (~~aspartic unit~~) or -CH₂-CH₂- (~~glutamic unit~~);

n' + m' or n' is defined as the degree of polymerization and varies from 10 to 1000 and preferably between 50 and 300.

9. (Currently amended) [[F]] The formulation according to claim 7 [[or 8]], characterized in that the [HG]₁ of the [PO] each independently of one another are a monovalent radical of the formula below:



in which:

R⁵ is a methyl (~~alanine~~), isopropyl (~~valine~~), isobutyl (~~leucine~~), sec-butyl (~~isoleucine~~) or benzyl (~~phenylalanine~~);

R⁶ is a hydrophobic radical containing from 6 to 30 carbon atoms;

l varies from 0 to 6.

10. (Currently amended) [[F]] The formulation according to claim 9, ~~characterized in that all or some of wherein at least one of~~ the hydrophobic radicals R⁶ of the [PO] [[arc]] is independently selected from the group of radicals ~~comprising consisting of~~:

a linear or branched alkoxy containing from 6 to 30 carbon atoms and ~~optionally~~ of containing at least one heteroatom (~~preferably O and/or N and/or S~~) and/or at least one unit of unsaturation,

an alkoxy containing 6 to 30 carbon atoms, having one or more fused carbocyclic rings and ~~optionally~~ containing at least one unit of unsaturation and/or at least one heteroatom (~~preferably O and/or N and/or S~~),

an alkoxyaryl or an aryloxyalkyl having 7 to 30 carbon atoms and capable of containing at least one unit of unsaturation and/or at least one heteroatom (~~preferably O and/or N and/or S~~).

11. (Currently amended) ~~[[F]]~~ The formulation according to claim 9 ~~[[or 10]],~~
~~characterized in that all or some of~~ wherein the hydrophobic radical R⁶ of the graft of the [PO]
is derived from an alcohol precursor selected from the group ~~comprising~~ consisting of: octanol,
dodecanol, tetradecanol, hexadecanol, octadecanol, oleyl alcohol, tocopherol and cholesterol.

12. (Currently amended) ~~[[F]]~~ The formulation according to claim 6, characterized in
that the [PO] ~~exists~~ comprises of an alpha-L-glutamate or alpha-L-glutamic homopolymer.

13. (Currently amended) ~~[[F]]~~ The formulation according to claim 6, ~~characterized in~~
~~that wherein~~ the [PO] ~~exists~~ comprises of an alpha-L-aspartate or alpha-L-aspartic
homopolymer.

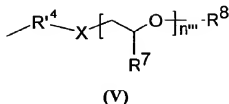
14. (Currently amended) ~~[[F]]~~ The formulation according to claim 6, ~~characterized in~~
~~that wherein~~ the [PO] ~~exists~~ comprises of an alpha-L-aspartate/alpha-L-glutamate or alpha-L-
aspartic/alpha-L-glutamic copolymer.

15. (Currently amended) ~~[[F]]~~ The formulation according to claim 14, ~~characterized~~
~~in that wherein~~, in the [PO], the distribution of the aspartic and/or glutamic units carrying grafts
containing at least one [HG] unit is such that the resulting polymer is either random or of the
block type or of the multiblock type.

16. (Currently amended) ~~[[F]]~~ The formulation according to claim 1, ~~characterized in~~
~~that wherein~~ the molecular weight of the [PO] is between 2000 and 100,000 g/mol and
~~preferably between 5000 and 40,000 g/mol.~~

17. (Currently amended) ~~[[F]]~~ The formulation according to claim 6, ~~characterized in~~
~~that wherein~~ the [PO] carries at least one graft of the polyalkylene glycol type bonded to a
glutamate and/or aspartate unit.

18. (Currently amended) ~~[[F]]~~ The formulation according to claim 17, ~~characterized~~
~~in that wherein~~ the graft of the polyalkylene glycol type has formula (V) below:



in which:

R⁴ is a direct bond or a "spacer" based on 1 to 4 amino acid units;

X is a heteroatom selected from the group comprising consisting of: oxygen, nitrogen and sulfur;

R⁷ and R⁸ independently are H or a linear C1 to C4 alkyl;

n''' varies from 10 to 1000 ~~and preferably from 50 to 300~~.

19. (Currently amended) [[F]] The formulation according to claim 17 [[or 18]], ~~characterized in that wherein~~ the polyalkylene glycol is a polyethylene glycol.

20. (Currently amended) [[F]] The formulation according to ~~any one of~~ claim [[s]] 17 [[to 19]], ~~characterized in that wherein~~ the molar percentage of polyalkylene glycol grafting varies from 1 to 30%.

21. (Currently amended) [[F]] The formulation according to claim 1 wherein any one of claims 1 to 20, characterized in that the hydrophobically modified polymers [PO] are selected from the group comprising consisting of: polyamino acids, polysaccharides (~~preferably those in the subgroup comprising pullulans and/or chitosans and/or mucopolysaccharides~~), gelatins and mixtures thereof.

22. (Currently amended) [[F]] The formulation according to claim 1, wherein any one of the preceding claims, characterized in that the AP is selected from the group consisting of: a protein, a glycoprotein, a protein bonded to one or more polyalkylene glycol chains [~~preferably polyethylene glycol (PEG) chains: "PEGylated protein"~~], a polysaccharide, a liposaccharide, an oligonucleotide, a polynucleotide [[or]] and a peptide; ~~said AP preferably being selected from haemoglobins, cytochromes, albumins, interferons, cytokines, antigens,~~

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~~antibodies, erythropoietin, insulin, growth hormones, factors viii and ix, interleukins or mixtures thereof, and haemopoiesis stimulating factors.~~

23. (Currently amended) ~~[[F]] The formulation according to claim 1, wherein any one of claims 1 to 21, characterized in that the active principle AP is a “small” hydrophobic, hydrophilic or amphiphilic organic molecule.~~

24. (Currently amended) ~~[[F]] The formulation according to claim 1, wherein any one of claims 1 to 22, characterized in that it's the weight fraction of AP not associated with the submicronic particles [non-associated AP], in weight %, is such that:~~

~~[non-associated AP] ≤ 1, preferably [non-associated AP] ≤ 0.5.~~

25. (Currently amended) ~~[[F]] The formulation according to claim 1 wherein any one of the preceding claims, characterized in that it the formulation is injectable by the parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour.~~

26. (Currently amended) ~~[[F]] The formulation according to claim 1 wherein any one of the preceding claims, characterized in that it the formulation is intended for the preparation of used to prepare drugs, particularly for administration by the parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour, or by the oral, nasal, vaginal or ocular route.~~

27. (Withdrawn -- Currently amended) Process for the preparation of drugs, particularly for administration by the parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour, or by the oral, nasal, vaginal or ocular route, ~~characterized in that it consists essentially in using comprising~~ at least one formulation according to ~~any one of claim~~ ~~[[s]] 1~~ ~~[[to 26]].~~

28. (Currently amended) ~~Δ~~ ~~[[D]] derived product, characterized in that it comprises comprising~~ submicronic particles formed of non-covalent PO/AP associations as defined in claim 1, and ~~in that it is obtained from the formulation according to any one of claim~~ ~~[[s]] 1~~ ~~[[to 26]].~~

29. (Currently amended) The [[D]] derived product according to claim 28, ~~said product is in characterized in that it consists of a powder or a gel form.~~

30. (Withdrawn -- Currently amended) A [[P]] process for the preparation of the formulation of claim 1, said process comprising the steps of: ~~according to any one of claims 1 to 26, characterized in that it consists essentially in:~~

taking a colloidal suspension of nanoparticles of at least one PO,
mixing this colloidal suspension of nanoparticles of PO with at least one AP,
preferably in aqueous solution, and
~~optionally adding at least one excipient,~~
adjusting the pH and/or the osmolarity if necessary, and
~~optionally filtering the resulting suspension.~~

31. (Withdrawn -- Currently amended) A [[P]] process according to claim 30, ~~characterized in that wherein the at least one AP is [[(are)]] in the form of an aqueous suspension or solution for mixing with the colloidal suspension of nanoparticles of PO.~~

32. (Withdrawn -- Currently amended) A [[P]] process for the preparation of the formulation of claim 1, said process comprising the steps of: ~~according to any one of claims 1 to 26, characterized in that it consists essentially in:~~

taking a powder of nanoparticles of at least one PO,
mixing this powder with an aqueous suspension or solution of at least one AP,
preferably in aqueous solution, and
~~optionally adding at least one excipient,~~
adjusting the pH and/or the osmolarity if necessary, and
~~optionally filtering the resulting suspension.~~

33. (Withdrawn -- Currently amended) A [[P]] process for the preparation of the formulation of claim 1, said process comprising the steps of: ~~according to any one of claims 1 to 26, characterized in that it consists essentially in:~~

taking a powder produced by drying the liquid formulation ~~according to~~
according to claim 1 ~~any one of claims 1 to 26,~~
mixing this powder with an aqueous liquid medium, and preferably with stirring,
~~optionally adding at least one excipient,~~
adjusting the pH and/or the osmolarity if necessary, ~~and~~
~~optionally filtering the resulting suspension.~~

34. (Withdrawn -- Currently amended) A ~~[[P]]~~ process for the preparation of a powder derived from the formulation of claim 1, wherein ~~according to any one of claims 1 to 26,~~ characterized in that said powder is obtained by drying the formulation of claim 1 ~~according to any one of claims 1 to 26.~~